



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكرو فيلم

بسم الله الرحمن الرحيم



HANAA ALY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم



شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



HANAA ALY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغييرات



يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



HANAA ALY

The Effect of Itraconazole on the Clinical Outcomes of Patients with Advanced Non Small Cell Lung Cancer Receiving Platinum Based Chemotherapy

Thesis

Submitted for Partial Fulfilment of MD Degree in Clinical Oncology & Nuclear Medicine

By

Asmaa Waheed Mohamed Mostafa

Under supervision of

Prof. Mohamed Mohamed El Bassiouny

*Professor of Clinical Oncology and Nuclear Medicine
Faculty of Medicine - Ain Shams University*

Dr. Dalia Abd El Ghani El-khodary

*Assistant Professor of Clinical Oncology and Nuclear Medicine
Faculty of Medicine - Ain Shams University*

Dr. Amr Shafik Tawfik

*Assistant Professor of Clinical Oncology and Nuclear Medicine
Faculty of Medicine - Ain Shams University*

Faculty of Medicine - Ain Shams University

2020



Let's start everything with

Bismillah





Acknowledgment



*First and foremost, I feel always indebted to **ALLAH**, the Most Kind and Most Merciful.*

*I'd like to express my respectful thanks and profound gratitude to **Prof. Mohamed Mohamed El Bassiouny**, Professor of Clinical Oncology and Nuclear Medicine - Faculty of Medicine- Ain Shams University for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

*I am also delighted to express my deepest gratitude and thanks to **Dr. Dalia Abd El Ghani El-khodary**, Assistant Professor of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shams University, for her kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

*I am deeply thankful to **Dr. Amr Shafik Jawfik**, Assistant Professor of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shams University, for his great help, active participation and guidance.*

*I wish to introduce my deep respect and thanks to **Dr. May Ahmed Shawki**, Lecturer of Clinical Pharmacy, Faculty of Medicine, Ain Shams University, for her kindness, supervision and cooperation in this study and it's publication.*

I would like to express my hearty thanks to all my family for their support till this work was completed.

Last but not least my sincere thanks and appreciation to all patients participated in this study.

Asmaa Waheed Mohamed Mostafa

List of Contents

Title	Page No.
List of Tables	i
List of Figures	v
List of Abbreviations.....	vii
Introduction	1
Aim of the Work.....	4
Epidemiology and Risk Factors.....	5
Pathology of Non-small Cell Lung Cancer & Clinical Presentation.....	14
Staging and Management of Metastatic NSCLC.....	24
Chemotherapy in Metastatic NSCLC	42
Patients and Methods.....	56
Results	61
Discussion	92
Summary	110
Conclusion	113
References	114
Arabic Summary	

List of Tables

Table No.	Title	Page No.
Table (1):	TNM descriptors for TNM-8 th edition.....	30
Table (2):	Changes made to TNM 7 th edition	31
Table (3):	Stages of lung cancer adapted from the 8th Edition of TNM in Lung Cancer.....	32
Table (4):	Five year survival of patients according to the T classification for pathologically and clinically diagnosed patients according to TNM-8	33
Table (5):	Ongoing clinical trials addressing ITZ as an adjunctive anticancer drug	55
Table (6):	Age distribution in all patients.....	62
Table (7):	Comparison between the two study groups regarding age distribution.....	62
Table (8):	Comparison between the two study groups regarding gender distribution	62
Table (9):	Comparison between the two study groups regarding performance state.....	63
Table (10):	Comparison between the two study groups regarding residence.....	63
Table (11):	Comparison between the two study groups regarding smoking habit.....	64
Table (12):	Comparison between number of packs of cigarette consumption among patients between the two groups	64
Table (13):	Comparison between study groups regarding Co-morbidities	65
Table (14):	Comparison between study groups regarding Family history of lung cancer.....	65
Table (15):	Comparison between study groups regarding tumor size and extension (T).....	66
Table (16):	Comparison between study groups regarding the side of the 1ry lung tumor.....	66

List of Tables *(Cont...)*

Table No.	Title	Page No.
Table (17):	Comparison between study groups regarding Nodal status (N)	67
Table (18):	Comparison between study groups regarding metastatic spread (M)	68
Table (19):	Comparison between the 2 study groups as regarding visceral versus bone metastasis	68
Table (20):	Distribution of tumor's pathology subtypes among the two study groups	69
Table (21):	Distribution of tumor's grade of differentiation among the two study groups	70
Table (22):	Immunohistochemistry: TTF1 expression among the two study groups	71
Table (23):	Immunohistochemistry: Ck7 expression among the two study groups.....	71
Table (24):	Immunohistochemistry: Carletinine expression among the two study groups:.....	71
Table (25):	Immunohistochemistry: P63 expression among the two study groups.....	72
Table (26):	Immunohistochemistry: EGFR state among the two study groups.....	73
Table (27):	Comparison between number of cycles of chemotherapy received between the study groups	73
Table (28):	Comparison between chemotherapy type between the study groups	74
Table (29):	Comparison between response rate between the study groups:	77
Table (30):	Comparison between Progression free survival (PFS) between the study groups.....	79
Table (31):	Comparison between overall survival (OS) between the study groups	80

List of Tables *(Cont...)*

Table No.	Title	Page No.
Table (32):	Multivariate analysis in terms of PFS in itraconazole arm.....	81
Table (33):	Multivariate analysis in terms of OS in itraconazole arm.....	82
Table (34):	Comparison between the study groups regarding haematological toxicity: Anaemia	83
Table (35):	Comparison between the study groups regarding haematological toxicity: neutropenia.....	84
Table (36):	Comparison between the study groups regarding haematological toxicity: Thrombocytopenia.....	84
Table (37):	Comparison between the study groups regarding non haematological toxicity: Vomiting.....	85
Table (38):	Vomiting incidence with cisplatin versus carboplatin in the control arm:	86
Table (39):	Vomiting incidence between cisplatin and carboplatin in itraconazole arm:.....	86
Table (40):	Comparison between the study groups regarding non haematological toxicity; Diarrhoea	87
Table (41):	Comparison between the study groups regarding peripheral neuropathy	87
Table (42):	Comparison between the study groups regarding non haematological toxicity: nausea.....	88
Table (43):	Comparison between the study groups regarding hepatic toxicity	89
Table (44):	Comparison between the study groups regarding cardiac toxicity.....	89

List of Tables (Cont...)

Table No.	Title	Page No.
Table (45):	Comparison between the two study groups regarding compliance on itraconazole.....	90
Table (46):	Comparison between the two study groups regarding Palliative radiotherapy either on 1ry lung tumor or bone metastasis.....	90

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Histological classification of NSCLC tumors	17
Figure (2):	Algorithm for antibodies employed by the Cleveland Clinic to direct the appropriate molecular testing on biopsy lung cancer specimens.....	19
Figure (3):	Image of FDG PET scan shows intense tracer concentration in the right hemithorax corresponding to a right lung mass.	26
Figure (4):	Treatment algorithm for advanced non squamous non-small cell lung cancer, wild type based on results of initial PD-L1 testing.....	36
Figure (5):	Treatment algorithm for advanced non squamous non-small cell lung cancer with EGFR mutation	39
Figure (6):	Schematic representation of the anticancer activity of ITZ.....	51
Figure (7):	Comparison between response rate after 2 cycles of chemotherapy between the study groups.....	75
Figure (8):	Comparison between response rate after 4 cycles of chemotherapy between the study groups.....	76
Figure (9):	Comparison between response rate after 6 cycles of chemotherapy between the study groups.....	76
Figure (10):	Overall response rate between the two groups	78

List of Figures *(Cont...)*

Fig. No.	Title	Page No.
Figure (11):	Kaplan-Meier curves of progression-free survival (PFS) comparison between the two study groups.	79
Figure (12):	Kaplan-Meier curves of 1-year overall survival (OS) comparison between the two study groups.	80
Figure (13):	Diagram of all documented toxicity in both groups.	91

List of Abbreviations

Abb.	Full term
<i>ABC</i>	<i>ATP-binding cassette</i>
<i>ABCB1</i>	<i>Transporter B1</i>
<i>ALK</i>	<i>Anaplastic lymphoma kinase</i>
<i>ALL</i>	<i>Acute lymphoblastic leukemia</i>
<i>AML</i>	<i>Acute myeloid leukemia</i>
<i>AMP</i>	<i>Association for Molecular Pathology</i>
<i>ASCO</i>	<i>American Society of Clinical Oncology</i>
<i>AUC</i>	<i>Area under the curve</i>
<i>BCC</i>	<i>Basal cell carcinoma</i>
<i>BRAF</i>	<i>B-Raf proto-oncogene</i>
<i>BSC</i>	<i>Best supportive care</i>
<i>CAP</i>	<i>The College of American Pathologists</i>
<i>ChT</i>	<i>Chemotherapy</i>
<i>CK5/6</i>	<i>Cytokeratin-5/6</i>
<i>CT</i>	<i>Computed tomography</i>
<i>DFS</i>	<i>Disease-free survival</i>
<i>EGFR</i>	<i>Epidermal growth factor receptor</i>
<i>EML4</i>	<i>Echinoderm microtubule-associated protein-like 4</i>
<i>EML4-ALK</i>	<i>Transforming anaplastic lymphoma kinase fusion gene</i>
<i>FDA</i>	<i>US Food and Drug Administration</i>
<i>F-FDG PET/CT</i>	<i>F-Fluorodeoxyglucose positron emission tomography/computed tomography</i>
<i>GCSF</i>	<i>Granulocyte colony stimulating factor</i>
<i>HR</i>	<i>Hazard ratio</i>
<i>HUVECs</i>	<i>Human umbilical vein endothelial cells</i>

List of Abbreviations *(Cont...)*

Abb.	Full term
<i>IASLC</i>	<i>International Association for the Study of Lung Cancer</i>
<i>IHC</i>	<i>Immunohistochemistry</i>
<i>ITZ</i>	<i>Itraconazole</i>
<i>KRAS</i>	<i>Kirsten rat sarcoma viral oncogene homolog</i>
<i>LC</i>	<i>Lung cancer</i>
<i>mTOR</i>	<i>Mechanistic target of rapamycin</i>
<i>NCCN®</i>	<i>National Comprehensive Cancer Network</i>
<i>NSCLC</i>	<i>Non-small cell lung cancer</i>
<i>OR</i>	<i>Odds ratio</i>
<i>ORR</i>	<i>Objective response rate</i>
<i>OS</i>	<i>Overall survival</i>
<i>PAHs</i>	<i>Polycyclic aromatic hydrocarbons</i>
<i>PD</i>	<i>Progression disease.</i>
<i>PD-1</i>	<i>Programmed cell death 1</i>
<i>PD-L1</i>	<i>Programmed death ligand 1</i>
<i>PFS</i>	<i>Progression-free survival</i>
<i>PM</i>	<i>Pemetrexed</i>
<i>PS</i>	<i>Performance state</i>
<i>PSA</i>	<i>Prostate-specific antigen</i>
<i>Qol</i>	<i>Quality of life</i>
<i>RCT</i>	<i>Randomized controlled trial</i>
<i>RD</i>	<i>Regression disease.</i>
<i>ROS1</i>	<i>ROS proto-oncogene 1</i>
<i>SCC</i>	<i>Squamous cell carcinoma</i>
<i>SCLC</i>	<i>Small cell lung cancer</i>
<i>SD</i>	<i>Stable disease.</i>
<i>SES</i>	<i>Socio-economic status</i>